International Journal of Gerontology 10 (2016) 96–99

Contents lists available at ScienceDirect

International Journal of Gerontology

journal homepage: www.ijge-online.com

Original Article

Modified Dang Gui Liu Huang Tang Eases Sleep Sweats in Elderly Patients with Terminal Cancer☆

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ARTICLE INFO

Article history:
Received 27 June 2013
Received in revised form
6 March 2015
Accepted 22 December 2015
Available online 28 May 2016

Keywords:
cancer,
hospice,
modified Dang Gui Liu Huang Tang,
sleep sweating

SUMMARY

Background: Patients with terminal cancer frequently suffer from sleep sweats, which occur while sleeping and cease after waking; the cause of these sweats is unknown. The aim of this study was to evaluate the efficacy of a modified Dang Gui Liu Huang Tang in managing sleep sweats, as well as to identify any associated adverse effects.

Methods: We enrolled 41 patients with terminal cancer who were receiving hospice care. We excluded patients whose sweating had known causes, as well as those taking drugs that can affect the sweating threshold. Patients received a modified Dang Gui Liu Huang Tang twice a day for 10 consecutive days.

Results: The quantitative assessment revealed that sleep sweating was completely relieved in 29 (70.7%) patients, and that the average time required for a 50% decrease in sweating was 5.3 days. Using a visual analog sweating scale that ranged from 0 to 10, patients and caregivers estimated that the mean decrease in sweating was 7.6 and 8.0, respectively. Furthermore, 78.0% of patients experienced an increased appetite after treatment. The most common adverse events were diarrhea (14.6%), nausea (12.1%), and allergy (2.4%), although the severity of these symptoms was never greater than Grade 2, and they resolved after the treatment was stopped.

Conclusion: The results suggest that the modified Dang Gui Liu Huang Tang is safe and effective in treating sleep sweats of an unknown cause in elderly patients with terminal cancer.

1. Introduction

Traditional herbal medicine is widely accepted and commonly used by Asians because of its safety, natural origin, and fewer adverse effects. Epidemiological surveys have shown that 44.6% of patients with cancer in Japan, and 31.4% in the USA, took complementary medicine during or after major cancer treatments[1,2].

Cancer is the leading cause of death in many countries; at its terminal stage, patients suffer from various complications, which often develop simultaneously[3–5]. The majority of these complications can be alleviated or eased using palliative medicines. However, several troublesome symptoms have no specific and effective treatment; sweating is one such symptom. Patients with terminal cancer often suffer from frequent sweating of unknown cause. For example, sleep sweats, which are characterized by sweating that develops while sleeping and ceases after waking, are particularly common in immunocompromised cancer patients. Such sweats usually render patients more susceptible to upper airway infections and resulting sepsis.

☆ Conflicts of interest: All contributing authors declare that they have no conflicts of interest.

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http://dx.doi.org/10.1016/j.ijge.2015.12.001

In traditional Chinese medicine (TCM), several effective herbal prescriptions are available for treating sleep sweats; these prescriptions are based on the different treatment principles used in TCM. The most commonly prescribed herbal medication for sleep sweats is Dang Gui Liu Huang Tang. This decoction functions to nourish "Yin", clear heat, and stabilize the exterior while stopping sweating. Some other symptoms that indicate Dang Gui Liu Huang Tang are fever, red face, dry mouth, dry parched lips, irritability, dry stools, constipation, and scanty dark urine. In addition, as confirmed by clinical observations, Fu Xiao Mai (*Tritici levis fructus*) and Mu Li (*Ostreae concha*) are also widely used to treat sweating. Therefore, we combined these two herbal drugs with Dang Gui Liu Huang Tang to form a modified prescription; we then evaluated the prescription's effectiveness. To our knowledge, no clinical evidence supports the use of this modified regimen to treat sleep sweats.

In the present study, we evaluated the efficacy of our modified Dang Gui Liu Huang Tang in treating sleep sweats, as well as the adverse events associated with the treatment. The study involved patients with terminal cancer who were receiving palliative care in a medical center-based hospice ward.

2. Materials and methods

2.1. Participants

Between January 2000 and February 2003, 41 biopsy-confirmed patients with cancer who were suffering from sleep sweats were enrolled in this prospective study. The other eligibility criteria were age > 60 years, ability to tolerate oral or nasogastric tube feeding, and receipt of palliative care in a medical center-based hospice ward. The exclusion criteria were as follows: fever > 37.5°C (aural), hypoglycemia, use of drugs that can affect the sweating temperature threshold (clonidine, pilocarpine, physostigmine, atropine, scopolamine, tramadol, or oral contraceptives), and bowel obstruction. The study was approved by the Institutional Review Board of the Mackay Memorial Hospital, Taipei, Taiwan (IRB Number: 13MMHIS050), and informed consent was obtained from all study participants.

2.2. Treatment regimen and protocol

Dang Gui Liu Huang Tang is a traditional therapy comprising drugs prepared from seven medicinal plants: Dang Gui (*Radix Angelicae sinensis*), Sheng Di Huang (*Epimedium sagittatum*), Shu Di Huang (*E. sagittatum*), Huang Qin (*Radix Scutellariae baicalensis*), Huang Lian (*Rhizoma Coptidis*), Huang Bai (*Cortex Phellodendri*), and Huang Qi (*Radix Astragali*). In our study, we modified Dang Gui Liu Huang Tang by adding two further herbal drugs that are widely used to treat sweating: Fu Xiao Mai (*Tritici levis fructus*) and Mu Li (*Ostreae concha*). The daily dose of the modified Dang Gui Liu Huang Tang was 9.0 g Dang Gui, 15.0 g Sheng Di Huang, 12.0 g Shu Di Huang, 9.0 g Huang Qin, 8.0 g Huang Lian, 8.0 g Huang Bai, 15.0 g Huang Qi, 11.25 g Fu Xiao Mai, and 15.0 g Mu Li. The herbs were chopped, and their extracts were obtained twice a day using 1000 mL of boiling water until 200 mL of liquid remained in the container. Each 200 mL herb concentrate was administered to the enrolled patients after breakfast and dinner for 10 consecutive days; a 1-hour interval was followed between the administration of the extracts and that of other drugs. We attempted to complete the entire course of this herbal regimen; however, the treatment was discontinued in cases where allergy, bowel obstruction, disturbance to consciousness, or death rattle developed.

2.3. Quantitative assessment of sleep sweats

Sweating was measured using a paper tissue absorption method. Twice each day—at 9:00 AM and 9:00 PM—10 layers of cut paper tissues (2 cm × 2 cm) were placed over an area of smooth skin on the right side of the neck (at the midpoint of the sternocleidomastoid muscle) and tightly covered using a 6 cm × 7-cm Tegaderm dressing (3M Health Care Co., Minneapolis, MN, USA). The change in the weight of the paper tissue was calculated immediately after its removal; the same well-trained physician's assistant both applied and removed the tissue. This evaluation was performed daily, starting on the day before treatment initiation, until the 10^{th} day of treatment.

2.4. Subjective estimation of sweating

The overall change in sweating symptoms was estimated by the patients and their caregivers using a visual analog scale (VAS) that ranged from 0 to 10.

2.5. Safety assessment

Safety evaluations were graded according to Version 2 of the Common Toxicity Criteria, published by the National Cancer Institute in 1998[6].

2.6. Data analysis

Data were expressed as mean ± standard error. Repeated measures analysis of variance was used to compare the amount of sweating with the subjective estimation of sweating over time. Statistical analyses were performed using the SPSS software package Version 18.0 (SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered significant.

3. Results

The characteristics of the 41 patients are presented in Table 1. In summary, the mean age of the study participants was 69.0 ± 6.4

Table 1
Characteristics of the study patients.

Characteristic	No. (%)
Sex	
Male	20 (48.8)
Female	21 (51.2)
Age (y), mean ± SD	69.0 ± 6.4
Male	67.0 ± 5.8
Female	71.0 ± 6.5
Primary site of tumor	
Head and neck	6 (14.6)
Lung	6 (14.6)
Breast	5 (12.2)
Cervical	5 (12.2)
Colon and rectal	4 (9.8)
Ovarian	3 (7.3)
Prostate	3 (7.3)
Liver	2 (4.9)
Endometrial	2 (4.9)
Esophagus	1 (2.4)
Gall bladder	1 (2.4)
Ureter	1 (2.4)
Lymphocyte	1 (2.4)
Primary unknown	1 (2.4)
With lymph node or distant metastasis	35 (85.4)

SD = standard deviation.

years; 48.8% were male and 51.2% were female. Around 85% of the patients had lymph node or distance metastasis.

The quantitative measurement revealed that sweating had completely resolved either during or after treatment in 29 of the 41 patients (70.7%). As shown in Figure 1, the mean sweating volume had decreased significantly over time ($p < 0.05$). The average time required to achieve a 50% decrease in sweating was 5.3 days.

In the 10 point VAS sweating score estimated by the patients and their caregivers, the mean decreases were 7.6 and 8.0, respectively. Figure 2 shows the changes in the VAS scores estimated by patients, while Figure 3 shows those estimated by their caregivers. On a different note, 78.0% of patients experienced an increase in appetite after the treatment.

The most common treatment-related adverse events were diarrhea (14.6%), nausea (12.1%), and allergy (2.4%); their severity was never greater than Grade 2. Furthermore, these complications resolved after cessation of treatment, and all 41 of the patients completed the study.

4. Discussion

In TCM, sleep sweats are both a symptom and a sign; they are characterized by sweating that develops while sleeping and stops after waking. In contrast, idiopathic sweating can develop at any time. Sleep sweats of unknown cause are a common symptom in patients with terminal cancer, comprising those sleep sweats that occur despite any underlying diseases and possible etiologies (infections, hypoglycemia, and use of drugs that may affect the sweating temperature threshold) being eliminated. They are not inherently life-threatening, but the resultant lack of sleep can cause further anxiety, as well as an increased risk of upper respiratory tract infections[7]. To date, no appropriate treatment for sleep sweats of unknown cause has been found.

Several pharmacological investigations have reported drugs that can affect the sweating temperature threshold. For example, oral contraceptive hormones cause this threshold to increase[8]. Conversely, the nitric oxide inhibitor N^G-nitro-L-arginine methyl ester (L-NAME)reduces sweating in horses during exercise[9], possibly because nitric oxide regulates cutaneous vasodilatation and thermoregulation[10–12]. It has also been reported that clonidine increases the sweating temperature threshold[13–15], whereas the narcotic analgesic tramadol decreases the threshold and has a slight thermoregulatory effect[16]. Nonetheless, in current palliative medicine, sleep sweats of unknown cause have no documented, effective treatment.

Dang Gui Liu Huang Tang is an herbal therapy commonly used in TCM to treat sleep sweats. The ingredients of the Dang Gui Liu Huang Tang used in this study were identical to those described in the Lan Shi Mi Chang (also known as the Secret Treasure of the Orchid Chamber)—an ancient medical book written by Li[17]. On the basis of previous clinical observations, we added two herbal drugs to the decoction, producing a modified prescription[18]. We then evaluated this medication's effectiveness. We found that the modified Dang Gui Liu Huang Tang was effective in treating patients with terminal cancer who had unexpected sweating, and that the treatment led to no significant adverse reactions. Furthermore, the increased appetite that occurred after administration of the modified Dang Gui Liu Huang Tang suggests that it promotes general well-being and quality of life in patients with cancer. Nonetheless, we could not determine whether the modified Dang Gui Liu

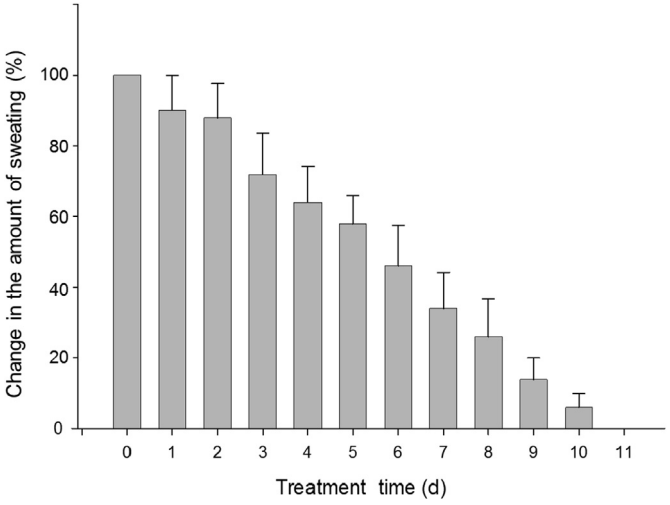

Figure 1. The amount of sweating was measured using a paper tissue absorption method. Data were collected from 41 individuals and expressed as mean ± standard error.

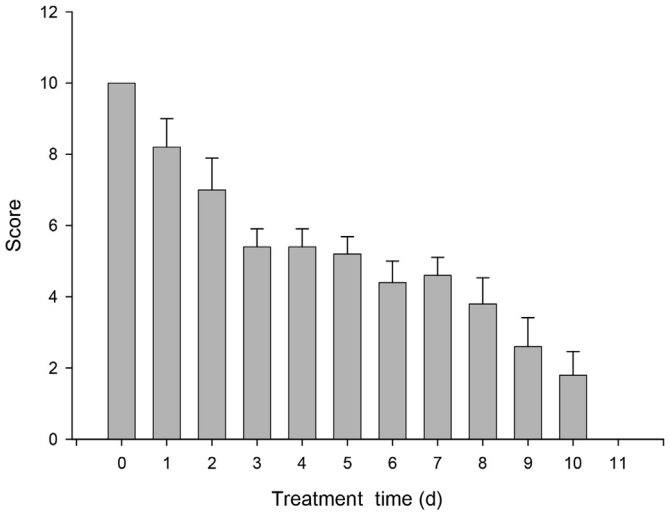

Figure 2. A visual analog scale sweating score was estimated by the patients. Data are expressed as mean ± standard error.

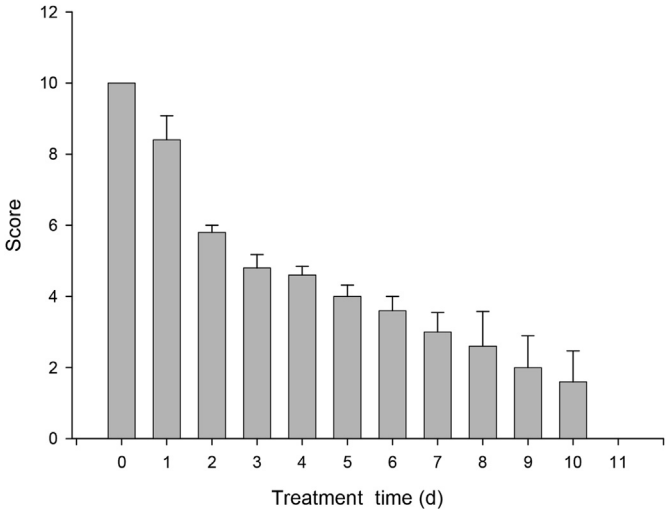

Figure 3. A visual analog scale sweating score was estimated by the caregivers. Data are expressed as mean ± standard error.

Huang Tang was superior to the original prescription, because we did not compare the two prescriptions in this study.

In TCM, Dang Gui Liu Huang Tang is administered to people with a generalized "Yin" deficiency. In modern medicine, the mixture may help improve general well-being and restore normal physical energy and function. Herbal therapists who are practitioners of TCM prescribe herbal remedies on the basis of individual physical conditions (e.g., body constitution or syndromes) after assessing patients on the basis of unique diagnostic systems. In this study, we administered a modified Dang Gui Liu Huang Tang to patients with sleep sweats. This strategy is not identical to that used in TCM; however, an herbal therapist working at the hospice ward examined all of the enrolled patients and found that 73.1% of the patients had a "Yin" deficiency syndrome according to TCM.

The results of this study indicate that modified Dang Gui Liu Huang Tang relieves sleep sweats of unknown cause in patients with terminal cancer, and that it increases appetite in those patients; the treatment is without any significant complications. Because this study was a nonrandomized trial, most of the enrolled participants were elderly patients. We therefore could not determine whether the modified Dang Gui Liu Huang Tang was more beneficial in patients of a particular age, or indeed if it was only effective in elderly patients. In future, randomized, double-blinded clinical trials are warranted to confirm the therapeutic effects of the treatment.

Acknowledgments

This study is supported in part by China Medical University Hospital, Taichung, Taiwan (DMR-104-085), and in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019) and China Medical University under the Aim for Top University Plan of the Ministry of Education, Taiwan.

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